CCR frontiers IN SCIENCE

July 2003, Volume 2 Published by the Center for Cancer Research, National Cancer Institute

Contents

NATIONAL CANCER INSTITUTE
NATIONAL INSTITUTES OF HEALTH
DEPARTMENT OF HEALTH AND HUMAN SERVICES

■ CANCER AND CELL BIOLOGY

A New Twist on Signal Transduction: The JAK/STAT Pathway Meets Cyclin-Cdk in *Drosophila*

Chen X, Oh SW, Zheng Z, Chen HW, Shin HH, and Hou SX. Cyclin D-Cdk4 and cyclin E-Cdk2 regulate the JAK/STAT signal transduction pathway in *Drosophila. Dev Cell* 4: 179-90, 2003.

In multicellular organisms, cell regulation is everything. Starting from the moment of sperm meeting egg, cells in the embryo send signals to each other to coordinate the growth of organs, limbs, and tissues. These signals involve cell fate determination; cell proliferation and differentiation; cell migration, convergence, and extension; and polarity determination. The communication signals regulating these processes have to be perfectly coordinated. Otherwise, disasters like cancer and other diseases can result. Studying the JAK/STAT signal transduction pathway in *Drosophila* provides an excellent opportunity to understand the molecular mechanism of cell regulation during embryonic development and tumor formation.

In mammals, the JAK/STAT cascade has emerged as an essential facet of signaling through a large number of cytokines and growth factors. These signals induce proliferation or cell fate determination and are crucial to the proper growth and development of mammalian tissues. Both decreases and increases in activity of this signaling pathway have severe consequences. Constitutive activation of JAKs, STATs, or both is correlated with several oncogenic transformations.

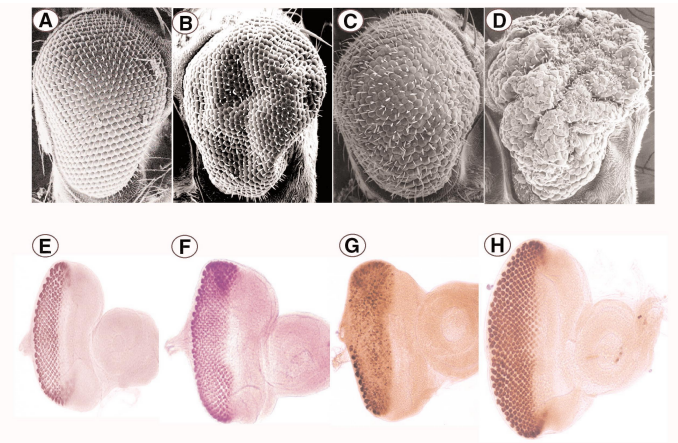

Figure 1. The *upd* and *CycD-Cdk4* genes synergistically regulate eye outgrowth. In these experiments we used the UAS/Gal4 technique to ectopically express genes in fly tissues. *GMR-Gal4* is an eye-specific driver. *Panels A–D* are scanned electron micrographs of adult eyes of the following phenotypes and genotypes: wild type (w^{1118}) (*A*), moderately deformed big eye (*GMR-Gal4/UAS-upd*) (*B*), larger ommatidia (*GMR-Gal4/UAS-CycD+UAS-Cdk4*) (*C*), and huge deformed eye (*GMR-Gal4/UAS-upd+UAS-CycD+UAS-Cdk4*) (*D*). *Panels E–H* show the onset of neuronal differentiation in the eye imaginal disc as revealed by staining for Elav. Compared with wild type (*E*), the disc of *GMR-Gal4/UAS-upd* larvae is bigger and has more ommatidia (*F*). Overexpression of *CycD* and *Cdk4* using the *GMR-Gal4* driver blocks cell differentiation (*G*). Co-overexpression of *upd*, *CycD*, and *Cdk4* by the *GMR-Gal4* driver dramatically increases disc size and number of ommatidia (*H*).

The basic mechanism of JAK/STAT signaling is as follows: a ligand (such as a cytokine) binds to a cell surface receptor, which interacts with JAK, a non-receptor tyrosine

kinase. JAK then phosphorylates the transcription factor STAT, which moves into the nucleus and regulates the expression of specific target genes. In *Drosophila*, the ligand is encoded by *unpaired* (*upd*; Harrison DA et al., *Genes Dev* 12, 3252-62, 1998), JAK is encoded by *hopscotch* (*hop*; Binari R and Perrimon N, *Genes Dev* 8, 300-12, 1994), and STAT is encoded by *stat92E* (also known as *marelle*, the French word for hopscotch; Hou XS et al., *Cell* 84, 411-9, 1996; Yan R et al., *Cell* 84, 421-30, 1996). The receptor is encoded by *master of marelle* (*mom*; Chen HW et al., *Genes Dev* 16, 388-98, 2002), a transmembrane protein with weak homology to mammalian cytokine receptors.

Since its discovery in *Drosophila* in 1996, the JAK/STAT signal transduction pathway has been shown to be required in an unusually broad set of developmental decisions (reviewed in Hou SX et al., *Dev Cell* 3, 765-78, 2002), including sex determination, polarity determination in the eye, male germline stem cell self-renewal, border cell migration in female germline, cell convergence and extension during posterior spiracle and hindgut formation, and fly innate immunity. Further, hyperactivation of this pathway leads to melanotic or leukemia-like tumor formation in the fly.

The numerous functions of the JAK/STAT pathway in *Drosophila* may result from its link to key cell regulators, such as cyclin-dependent kinases and their associated cyclins. Using a large-scale genetic screen, we recently identified the *Drosophila* cyclin-dependent kinase 4 (*Cdk4*) as a component of the JAK/STAT signal transduction pathway. *Cdk4* flies exhibit embryonic mutant phenotypes identical to those in the Hop/JAK kinase and *stat92E*/STAT mutations. Specific genetic interactions between *Cdk4* and *hop* mutations suggest that Cdk4 functions downstream of the HOP tyrosine kinase. We further showed that cyclin D (CycD)-Cdk4 and cyclin E (CycE)-Cdk2 bind and regulate STAT92E protein stability. STAT92E regulates gene expression for various biological processes, including the endocycle S phase. In the eye, excess HOP/STAT92E signaling induces cell overproliferation and excess CycD-Cdk4 activity blocks differentiation and induces overgrowth (Figure 1). We have shown that excess HOP/STAT92E signaling can synergize with both CycD-Cdk4 and CycE-Cdk2 in melanotic tumors but specifically synergizes with CycD-Cdk4, not CycE-Cdk2, to promote formation of an enlarged eye with extra ommatidia. These results demonstrated that the JAK/STAT pathway and cyclin-Cdk cooperatively regulate tissue outgrowth and tumor formation in *Drosophila*.

Although it remains to be seen whether cooperation of CycD-Cdk4 and the JAK/STAT pathway in regulating tissue growth is a general phenomenon in all species, abundant evidence shows that CycD-Cdk4 and the JAK/STAT pathway regulate similar biological processes in both the fly (reviewed in Hou SX et al., *Dev Cell* 3, 765-78, 2002) and mammals (reviewed in O'Shea JJ et al., *Cell* 109, S121-S131, 2002; Levy DE and Darnell JE Jr, *Nat Cell Biol* 3, 651-62, 2002). Just as overexpression of CycD-Cdk4 in the fly wing or eye causes hyperplasia, targeted overexpression of CycD1 in mice can promote epidermal, mammary, and thymic hyperplasia. These parallels are also evident in loss-of-function studies. Both CycD1 and Cdk4 knockout mice are smaller than their littermates and exhibit decreased growth rates. Cdk4-mutant flies are also small. Both male and female Stat5a/b-deficient mice are small, with reduced fat pad size and insulin-like growth factor 1 level. In *Drosophila*, strong alleles of *upd* are embryonic lethal, and weaker alleles such as os^{1} and os^{s} give rise to adult flies with small eyes. Complete loss of *hop* activity results in the absence of proliferating diploid imaginal cells throughout the larva, and some transheterozygous combinations of alleles give rise to adults with a small eye or eyeless phenotype. Taken together, these observations suggest that both CycD-Cdk4 and the JAK/STAT pathway regulate tissue growth.

Further, in the fly, two dominant temperature-sensitive mutations that hyperactivate HOP, $hop^{Tum\text{-}l}$ and hop^{T42}, lead to melanotic or leukemia-like tumor formation. Germline mutations in human Cdk4, a result of the Arg24Cys substitution which abrogates the inhibition of Cdk4 activity by its inhibitor, $P16^{INK4a}$, have been identified in familial melanoma (Wolfel T et al., *Science* 269, 1281-4, 1995; Zuo L et al., *Nat Genet* 12, 97-9, 1996). Mice with the R24C mutation display an increased weight of 5 to 10 percent compared with control littermates. However, $Cdk4^{R24C/R24C}$ mice did not develop melanoma similar to that observed in humans carrying the same R24C mutation in *Cdk4* (Rane SG et al., *Nat Genet* 22, 44-52, 1999).

It is likely that predisposition to melanoma requires a second cooperative signal. The JAK/STAT signaling may identify the second signal. The collaboration of *upd* and *CycD-Cdk4* in the fly eye may somehow mimic signal cooperation during tumor formation. On the one hand, *CycD-Cdk4* promotes cell growth and blocks cell differentiation; on the other hand, *upd* stimulates cell proliferation. Cooperation of the two signals results in a dramatically outgrown tumor-like eye.

More than 80 percent of cancers have detectable lesions in one component of the Cdk4 complex (Cdk4, INK4a, D1, and RB) (Sherr CJ and Roberts JM, *Genes Dev* 13, 1501-12, 1999). Many growth factors and components of signal transduction are oncogenes. Our recent results showed that CycD-Cdk4 and the HOP/STAT92E pathway collaboratively induce tissue overgrowth and melanotic tumor formation. We suggest that this relationship between coordinated STAT and cyclin-Cdk signaling could regulate cell fate, the cell cycle, or tumor progression in mammals as well. Thus, the powerful genetic manipulations available in *Drosophila* may make this an ideal system to study cancer.

- **Xiu Chen, PhD**
  Visiting Fellow
- **Steven Hou, PhD**
  Principal Investigator
  Laboratory of Immunobiology
  NCI-Frederick, Bldg. 560/Rm. 12-70
  Tel: 301-846-1589
  Fax: 301-846-6145
  shou@mail.ncifcrf.gov

The Clinical Studies Support Center: Linking Eligible Patients to NCI Clinical Studies

Competition for clinical trial participants has increased dramatically in the past decade. Throughout the nation, many oncologists who once referred their patients to NCI now have more clinical trial options at their own institutions and at other hospitals. As a result, a concerted approach to promoting NCI intramural clinical trials has become necessary.

The Cancer Information Service (CIS) has long provided personalized information to callers about all clinical studies—not only NCI-sponsored clinical studies. Not part of the CIS mandate, however, is specific study promotion of NCI intramural studies. Therefore, NCI established the Clinical Studies Support Center (CSSC) in 1998 to help raise awareness of its intramural clinical trials through outreach and specialized study promotion efforts.

The CSSC uses a variety of outreach strategies to help CCR Principal Investigators promote individual clinical studies and study groups. The CSSC's call center is a point of contact for these promotions—helping callers to identify CCR trials that may be appropriate for the patient, providing detailed information about trial options in Bethesda, and referring patients to a CCR study contact or the CIS to learn about other potential options. Highly trained information specialists at the call center conduct tailored searches of clinical studies, facilitate communication with referring physicians and NCI researchers, and forward study summaries to callers. They also pre-screen some callers for specific clinical trials and forward the results to study coordinators.

Since its inception, the CSSC has experienced tremendous growth. In the program's first 4 years, the volume of calls more than doubled, from 4,789 to 9,660. Last year the number of people contacting the call center reached nearly 15,000 (Figure 1). The steady rise in callers suggests the CSSC is an increasingly recognized and consulted resource for information on cancer clinical trials.

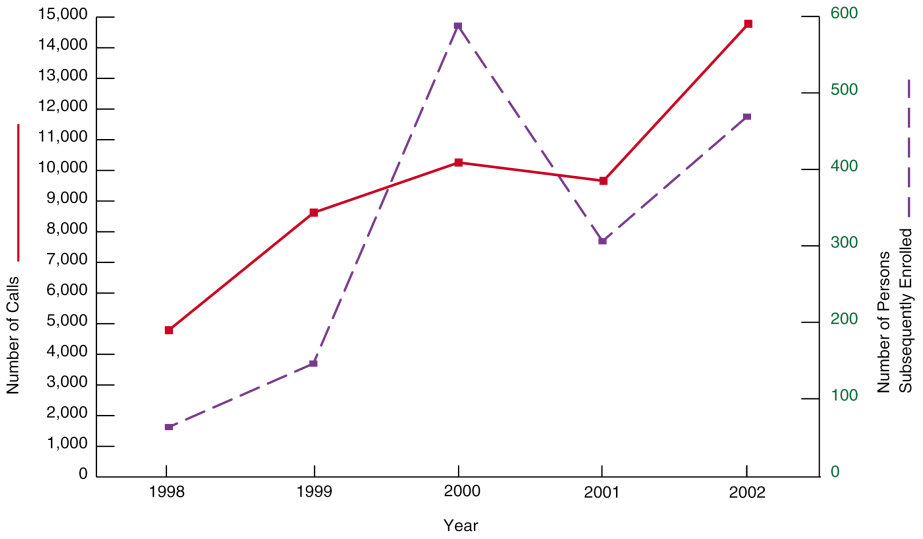

Figure 1. Number of calls to CSSC and number of persons subsequently enrolled in an NCI clinical trial, 1998–2002.

In the first 5 months of 2003 alone, the call center's services resulted in 120 referrals to the Neuro-Oncology Branch, 171 to the Surgery Branch, 66 to the Pediatric Oncology Branch, and 644 to other NCI Principal Investigators. Intense public interest in cancer genetics resulted in 75 referrals to genetics studies in a single month (March 2003).

While calls to the CSSC have tripled since 1998, the number of callers who subsequently enrolled in NCI clinical trials climbed sevenfold during that period (Figure 1). These considerable gains have been complemented by the CSSC's outreach efforts. The CSSC distributed a total of 57,045 copies of trial protocols for 366 different studies between April 1998 and March 2003. For Principal Investigators, such efforts mean improved community awareness of NCI's intramural studies program and, ultimately, meeting enrollment goals more quickly.

***CCR Frontiers in Science*—Staff**

Center for Cancer Research
J. Carl Barrett, PhD, *Director*
Kathryn Zoon, PhD, *Principal Deputy Director*
Frank M. Balis, MD, *Clinical Director*
L. Michelle Bennett, PhD, *Associate Director for Science*

Deputy Directors
C. Norman Coleman, MD
Lee J. Helman, MD
Douglas R. Lowy, MD
Robert H. Wiltrout, PhD
Stuart H. Yuspa, MD

Editorial Staff
Tracy Thompson, *Editor-in-Chief*
Sue Fox, BA/BSW, *Senior Editor*
Lizzie Hess, ELS(D), *Managing Editor**
Ave Cline, *Editor*
Kay Fleming, PhD, *Writer*
Karen Harris, MPH, *Writer***
Rob Wald, *Publications Manager**
Michael Fleishman, *Graphic Artist**

*Palladian Partners, Inc.
**Matthews Media Group, Inc.

Resurrection in the Thymus

Khaled AR, Li WQ, Huang J, Fry TJ, Khaled AS, Mackall CL, Muegge K, Young HA, and Durum SK. Bax deficiency partially corrects interleukin-7 receptor alpha deficiency. *Immunity* 17: 561-73, 2002.

Interleukin 7 (IL-7) is a cytokine produced by stromal cells in lymphoid organs. Severe lymphoid deficiencies result from defects in the IL-7 receptor (IL-7R) pathway in humans and knockout mice. IL-7 was originally discovered as an activity in stromal cell supernants that induced growth of immature B lymphocytes. Our laboratory and others explored the concept that, rather than inducing cell proliferation, IL-7's main physiological activity is actually "trophic"—that is, maintaining cell survival without proliferation. We and others found that much of this trophic activity could be attributed to IL-7–inducing synthesis of Bcl-2, a protein that inserts in the mitochondrial outer membrane and protects mitochondria from a variety of insults.

If IL-7 induces synthesis of Bcl-2, thereby protecting mitochondria, what is IL-7 protecting them from? One candidate is Bax, a protein related to Bcl-2 but with opposing effects: Bax damages mitochondria, and Bcl-2 counters this damage. We found that immature thymocytes, which are highly dependent on IL-7, contain a lot of Bax, but it is very difficult to perform cell biology studies using immature thymocytes, which are rare and fragile cells. Fortunately we were able to develop an IL-7–dependent thymocyte cell line from a p53-knockout mouse and eventually identified a pathway leading from IL-7 withdrawal to the activation of Bax. This pathway is as follows: 1) IL-7 withdrawal activates p38 stress kinase, 2) p38 phosphorylates NHE1, a transmembrane ion exchanger that regulates intracellular pH, 3) NHE1 elevates cytosolic pH to extremely high levels of pH 8 and higher, 4) alkaline pH induces a conformational change in cytosolic Bax, and 5) Bax translocates to mitochondria, inserting in the mitochondrial outer membrane. This sequence of events occurs over 6 hours and we verified it also occurs in immature thymocytes deprived of IL-7. But a critical issue was whether this Bax activation process is really a major killer of thymocytes or is just one of many injuries to a cell deprived of its trophic factor.

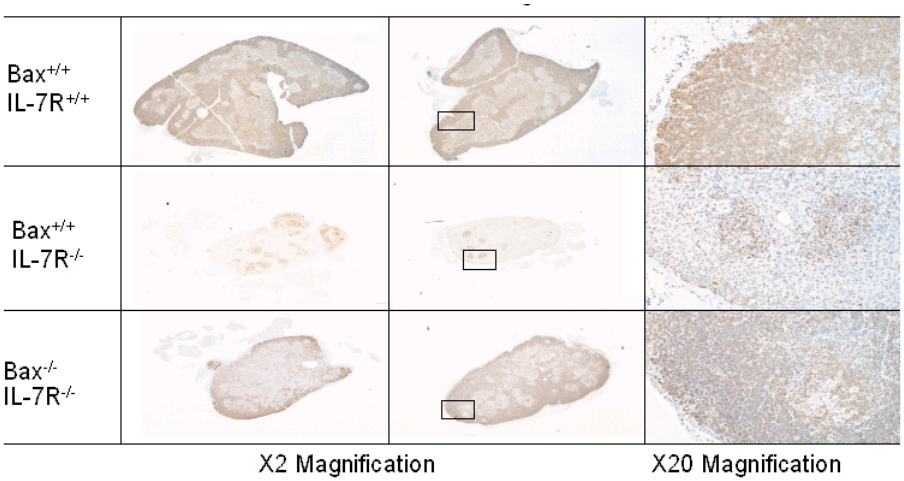

Figure 1. Anti-CD3 staining showing restoration of thymocyte development by deletion of Bax from interleukin 7 receptor (IL-R7)–deficient mice.

We then showed that the Bax death process is actually the major pathway to killing cells deprived of IL-7 during thymocyte development, at least in embryos and young mice. The approach was to try, by introducing an additional deletion in Bax, to cure a mouse that had a deletion of its IL-7R and was severely depleted in thymocytes. Both the Bax and IL-7R knockout mice preexisted, yet this simple approach actually took 2 years to get the first double knockout mouse, partly because Bax-deficient homozygotes are sterile and partly because it desecrated Mendel's rules. To our delight, we finally analyzed the first mice deficient in both IL-7R and Bax and found that the main lineage of thymocytes, $\alpha\beta$ cells, was restored (Figure 1). Bax deletion had many of the same effects others had shown for introducing a Bcl-2 transgene, meaning that Bax must be the major counterpart to Bcl-2 in the IL-7 pathway.

Thus Bax was shown to be a key component in this death pathway in the embryo and young mouse, and it was gratifying that the death pathway we had worked out in a cell line was of physiological significance. By a few months after birth, however, the thymus of $Bax^{-/-}IL\text{-}7R^{-/-}$ mice had reverted to a depleted state as severe as in $IL\text{-}7R^{-/-}$ mice, demonstrating that there must be an additional, non-Bax death pathway that develops. Evidence indicated that some other death proteins (Bad, Bim, and Bak) could also be involved. Moreover, we have found a number of metabolic disturbances in cells deprived of IL-7 that could be important, such as cytosolic alkalinization, severely impaired glucose import, impaired ADP import into mitochondria, and impaired ATP synthesis.

Most of the cells in the body probably depend on survival signals that thereby regulate tissue dimensions. Our hope is that the IL-7R pathway to cell survival is representative of trophic signaling in

general. We find that several features we identified following IL-7 withdrawal (stress, alkalinization, and Bax translocation) also occur in cells dependent on other trophic receptors, such as interleukin 3 and nerve growth factor. Metastatic cancer cells can survive outside their normal microenvironment, and several components of the IL-7R pathway are involved in oncogenesis, such as Bcl-2 and Bax. Thus, probing the trophic pathways may reveal new molecular targets for chemotherapeutics.

■ **Howard A. Young, PhD**
Principal Investigator
Laboratory of Experimental Immunology
youngh@mail.ncifcrf.gov

■ **Scott K. Durum, PhD**
Principal Investigator
Laboratory of Molecular Immunoregulation
NCI-Frederick, Bldg. 560/Rm. 31-71
Tel: 301-846-1545
Fax: 301-846-6720
durums@mail.ncifcrf.gov

Regulation of Innate and Adaptive Immunity with Endogenous Antimicrobial Peptide

Biragyn A, Ruffini PA, Leifer CA, Klyushnenkova E, Shakhov A, Chertov O, Shirakawa AK, Farber JM, Segal DM, Oppenheim JJ, and Kwak LW. Toll-like receptor 4-dependent activation of dendritic cells by beta-defensin 2. *Science* 298: 1025-9, 2002.

Microbial invasion induces the production of a plethora of proinflammatory cytokines and other regulatory factors of innate immunity, including small antimicrobial peptides called defensins (Medzhitov R and Janeway CJ, *N Engl J Med* 343: 338-44, 2000). This activation involves signaling via ancient pattern recognition by cell surface protein receptors such as the Toll-like receptors (TLRs), a type I transmembrane receptor family first discovered in fruit flies and whose cytoplasmic region shares homology with mammalian interleukin 1 receptor. TLRs are expressed differentially on immune cells and differ by their specificity for a variety of microbial components (Akira S et al., *Nat Immunol* 2: 675-80, 2001).

Defensins are divided into the α- and β-defensin subfamilies. Twenty-eight new human and 43 new mouse β-defensin genes have been identified as clusters in five syntenic chromosomal regions. The first hint that β-defensin might have functions other than antimicrobial activity was reported by D. Yang and colleagues (*Science* 286: 525-8, 1999), who demonstrated that human β-defensin 2 induced migration of immature dendritic cells (DC) via the chemokine receptor CCR6. Recently, our laboratory, together with our collaborators, proposed that murine β-defensin 2 may also have direct effects on adaptive immunity by activating DC maturation and regulating expression of Th1 cytokine responses and demonstrated that this effect is mediated by signaling through TLR-4. Although TLRs may use other endogenous molecules produced during stress or cell damage—such as heat shock proteins, fibronectin fragments, and hyaluronan—this was the first demonstration that an antimicrobial peptide produced during inflammation can serve as an endogenous ligand for TLR-4.

Our studies, which originally used genetic fusions of β-defensins and chemokines with nonimmunogenic tumor and HIV antigens to target antigen delivery to immature DC *in vivo* as vaccines, unexpectedly revealed that the resulting immune responses differed substantially depending on the type of chemoattractant moiety used. In particular, murine β-defensin 2-based vaccines elicited only modestly higher levels of antigen-specific antibodies than unfused vaccines did, but very potent cell-mediated and antitumor immunity (Biragyn A et al., *J Immunol* 167: 6644-53, 2001; Biragyn A et al., *Blood* 10: 1153-9, 2002). Therefore, we hypothesized that the ability of β-defensin 2 to augment cell-mediated immune responses may be due to specific effects on immature DC. To test whether β-defensins had any direct effect on DC function, bone marrow-derived immature DC were incubated with various fusion proteins consisting of murine β-defensin 2 or 3, or controls, linked to a lymphoma antigen. Murine β-defensin 2, but not 3, specifically induced DC maturation, as demonstrated by increased expression of cell surface markers (such as B7.2, CD40, $CD11c^+$, and major histocompatibility class II) and proinflammatory Th1-specific cytokines. Using immature DC isolated from various *TLR-4* mutant or knockout mice, we concluded that the signaling receptor for murine β-defensin 2-induced DC maturation was TLR-4. These data were further confirmed by activation of reporter genes in *TLR-4*–transduced cells.

Thus, the direct activation of DC by defensins, in turn, augments T-cell responses *in vitro* and triggers type 1 polarized adaptive immune responses *in vivo*. Defensins may play an important role in immunosurveillance against pathogens and, possibly, self-antigens or tumor antigens. Finally, the natural adjuvant property of defensins may be exploited for the development of more effective vaccines and immunotherapeutics by, for example, targeting antigen delivery to receptors on immature DC *in vivo*.

■ **Larry W. Kwak, MD, PhD**
Principal Investigator
Experimental Transplantation and Immunology Branch
NCI-Frederick, Bldg. 567/Rm. 205
Tel: 301-846-1607
Fax: 301-846-6107
kwak@mail.ncifcrf.gov

The NCI and the FDA: Good Science, Regulation, Collaboration, and Cooperation

Collaboration between CCR researchers and their counterparts in the Food and Drug Administration (FDA) will enhance our ability to attain NCI's goal of eliminating death and suffering due to cancer by 2015. The FDA regulates all drugs, biological agents, and devices used to prevent, screen for, diagnose, treat, and monitor the disease. Thus, our ability to develop new products or combinations of products that will alleviate death and suffering in cancer patients requires that we work closely with the FDA to promote the best science, develop safe and effective means to prevent cancer, and diagnose, treat, and monitor patients. As we develop the next generation of interventions—including molecularly targeted agents, genomic- and proteomic-based screening or diagnostic tools, and enhanced imaging or delivery systems—our ability to translate innovations into the clinic will depend on their successful evaluation by the FDA.

The FDA's mission ranges from reviewing all clinical research involving human subjects to approving and overseeing the use of medical products. It exercises "pharmacovigilance" and product quality oversight over all medical products from their conception until they are no longer marketed. The agency's components include five product review centers (Centers for Biologics Evaluation and Research [CBER], Devices and Radiological Health, Drugs Evaluation and Research, Food Safety and Applied Nutrition, and Veterinary Medicine), the Office of Regulatory Affairs, the National Center for Toxicological Research, and the Office of the Commissioner.

Each component's regulatory functions are based on sound science, law, and public health policy. Their activities include research on regulatory issues, reviews of sponsor submissions,

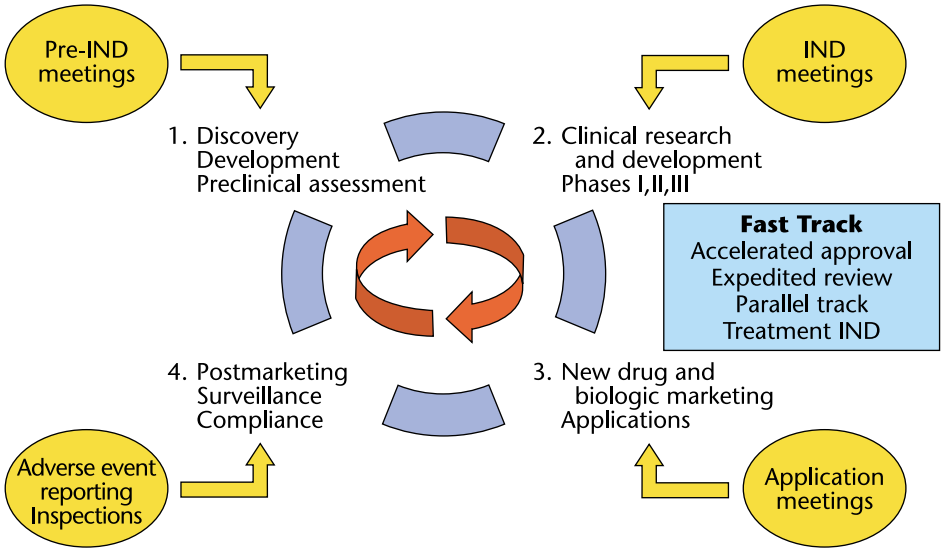

Figure 1. Drug and biologic development cycle.

development of new policies and regulations, surveillance of medical products, and monitoring of sponsor compliance.

Two laws form the foundation of FDA regulation, the Public Health Service Act and the Food, Drug, and Cosmetic Act. FDA regulations constitute the agency's interpretation of these laws. Regulations for medical products are recorded in Title 21 of the Code of Federal Regulations. In addition, the FDA publishes guidances, such as "Guidance for Industry" and "Fast-Track Drug Development—Designation, Development, and Application Review," to facilitate product development. The agency has also published guides related to international harmonization standards on the quality, safety, and efficacy of biologics and drugs. Recognizing the need for international standards to ensure the safety and efficacy of therapeutic agents, the FDA became one of the six founding members of the International Conference on Harmonisation in 1990.

The FDA is involved in every stage of the drug and biologic development cycle, beginning with the formulation of plans to introduce a therapeutic agent (in FDA parlance, an "investigational new drug" or IND) into human testing (Figure 1). The fast track is a program for the development of new drugs and biologics for severe and life-threatening illnesses for which there are no alternative therapies. It applies to cancer as well as many other diseases.

Good science and communication at every level—from discovery through the post-marketing phase—are key to successful interactions with the FDA and are crucial if development and review are to be accomplished in a timely manner. Sponsors of regulatory submissions should focus on questions related to product manufacturing and testing, pharmacology, toxicology, and clinical trial design and analysis. They must also demonstrate adherence to Good Laboratory Practices, Good Manufacturing

Practices, Good Clinical Practices, and other forms of guidance.

Basic science discoveries, translational research including standards and methods development, testing in pre-clinical models, and well-designed clinical trials are fundamental to all advances in medical products that successfully make the transition into the clinic. These elements represent critical points where collaboration between the NCI and the FDA will prove most fruitful. The science base of the NCI, represented by the CCR and extramural research programs, can enhance the scientific review capacity of the FDA. Concomitantly, the FDA's product development skills can augment the Institute's capacity to translate its discoveries to public benefit.

Under Dr. von Eschenbach's leadership, the NCI has formed an Oncology Task Force consisting of representatives from both agencies that will examine a range of issues, including biomarkers and surrogate end points, training and joint appointments, research collaborations, methods and standards development, and special topics related to oncology product development. To further cooperation, the CCR has entered into two Interagency Agreements with the FDA. The first constitutes the joint NCI/FDA Clinical Proteomics Program led by Lance Liotta, MD, PhD, of the CCR/NCI and Emanuel Petricoin, PhD, of the CBER/FDA. Established 4 years ago, the program has recently set up a reference laboratory to expedite the delivery of proteomic-based diagnostic technologies into the clinic. A second interagency agreement has recently been negotiated: the CBER/NCI Microarray Program for the Quality Assurance of Cancer Therapies and Other Biological Products. Together, these programs offer a compelling paradigm for future cooperation. Given their commitment to science and public health, we can expect that the NCI and the FDA will collaborate effectively to ensure we reach the goal of eliminating death and suffering due to cancer by 2015.

As we develop the next generation of interventions, our ability to translate innovations into the clinic will depend on their successful evaluation by the FDA.

For more information, visit the agency's website at www.fda.gov.

■ **Kathryn C. Zoon, PhD**
Principal Deputy Director

■ ADMINISTRATIVE LINKS

Fellows Editorial Board (FEB)
Even the greatest scientific achievements must be effectively communicated to exert a significant impact. The NCI/CCR Fellows Editorial Board (FEB) provides a free and confidential editing service to NCI/CCR fellows. FEB is composed of professional scientists and science writers trained in scientific editing who will carefully edit your document for grammar, structure, and style (they do not comment on the science!). Their collective comments will be returned to you within 10 business days of your submission, and the content of your document will be kept strictly confidential. Let FEB help you put your abstract, manuscript, grant proposal, or clinical protocol into the best possible form so that your readers can focus on the importance of your results and ideas and you can get published or funded. For more information or if you would like to become an FEB member, e-mail us at ncieditors@mail.nih.gov or visit our website at http://ccr.cancer.gov/careers/feb/.

Ethics Requirements: Reporting Deadlines
Those staff members who are required to complete various documents for the NCI Ethics Office should note the deadlines below.

- Financial Disclosure Reports: October 31;
- Annual Ethics Training: December 31;
- Annual Reconciliation Documents (ongoing outside activities, approved official duty appointments with outside organizations, and recusals): These documents must be reviewed by the employee and returned to the NCI Ethics Office in the spring of each year.

For more information, contact Diane Christensen at Christdi@mail.nih.gov.

NCI Quality of Work/Life Programs
The Office of Diversity and Employment Programs (ODEP) provides information on a variety of NCI programs, services, and guidelines that can enhance the quality of your work life and help you balance your personal and professional concerns. Explore options such as Flexitime, Compressed Work Schedule (CWS), and Telework by visiting the ODEP website at http://camp.nci.nih.gov/admin/odep/qwl/index.html.

***CCR Frontiers in Science*: Online and Hard Copies**
Current and archived issues (PDFs) of *CCR Frontiers in Science* can be viewed or printed by going to http://ccr.cancer.gov/news/newsletter.asp. Please contact Ave Cline at acline@mail.ncifcrf.gov if you would like to receive additional hard copies for your group.

Raffit Hassan, MD

Raffit Hassan, MD, joined the CCR's Laboratory of Molecular Biology in August 2002 as a tenure-track principal investigator. Born in Kashmir, India, he graduated from Government Medical College Srinagar, University of Kashmir. He did his internship and residency in internal medicine at Sisters Hospital, State University of New York at Buffalo. After completing his residency training he joined the medical oncology fellowship program at NCI. For the laboratory part of his fellowship he worked in the laboratory of Dr. Ira Pastan, chief of the laboratory of molecular biology, whose lab is focused on treating cancers using recombinant immunotoxins. Dr. Hassan's research involved exploiting mesothelin, a cell surface protein present on normal mesothelial cells and highly expressed in several tumors, as a candidate for tumor-specific therapy of ovarian cancer and mesotheliomas. His laboratory studies showed that mesothelin was a promising candidate for targeted therapy because the anti-mesothelin monoclonal antibody specifically localized in mesothelin-expressing tumors and because an immunotoxin targeting mesothelin had significant anti-tumor activity *in vitro* and *in vivo*.

After completing his oncology fellowship training, Dr. Hassan joined as an Assistant Professor of Medicine at the University of Oklahoma. His research showed that SS1(dsFv)PE38, a recombinant anti-mesothelin immunotoxin, was cytotoxic to mesothelin-positive tumor cells obtained from patients with ovarian cancer and peritoneal mesotheliomas. Subsequently, at the University of Oklahoma he started a Phase I study of SS1(dsFv)PE38 for mesothelin-expressing ovarian cancers and mesotheliomas, a study he will be completing at the NCI Clinical Center. After completion of the Phase I study he plans to initiate Phase II studies of SS1(dsFv)PE38 for pancreatic cancer, ovarian cancer, and mesotheliomas. In addition, his laboratory studies are focused on improving the efficacy of antibody-based therapies by increasing delivery to solid tumors, with the goal of translating these findings to the clinic.


Dr. Hassan

Dr. Hassan's work has been supported by several peer-reviewed grants. In 2001 he received the American Society of Clinical Oncology Career Development Award. Dr. Hassan was also awarded the NIH Mentored Patient-oriented Research Career Development Award, which came with grant support for 5 years, in 2002. Dr. Hassan lives with his wife Rubina Mattu, a pathologist, and their two sons.